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Abstract

In this paper, we describe a monodomain model with a non-local source term that accounts for any intra- or extracellular applied current, and specifically for the usual virtual electrode polarization phenomena, at no additional cost. The source term is derived from a lifting principle applied to the resolution of the electrostatic balance equation in the parabolic-elliptic formulation of the bidomain equations.

1. Introduction

The response of the heart to an external electrical current stimulus remains a very active subject of research, for instance in the quest of understanding defibrillation mechanisms [1]. The well known virtual electrode polarization (VEP) phenomena play a very important role in this area [2, 3].

The VEP mechanisms are known to be related to the complex anisotropic fiber structure of the heart and an unequal anisotropy ratio between the intra- and extra-cellular tissue compartments. For these reasons, the bidomain equations seem the most adapted model of the heart electrical activity in this case [4]. Indeed, the monodomain equations do not describe both the intra- and extracellular media, although solving these equations is about ten times faster than the solving the bidomain ones [5].

In this paper, we show how to derive a monodomain approximation of the bidomain equations in the presence of intra- or extra-cellular current stimulations. Indeed, the electrostatic balance between the intra- and extracellular media, that characterizes the bidomain equations, is linear. Following the superposition principle, we split its solution into a propagation part, that is approximated by a monodomain model, and an excitation part, that remains unchanged. Equivalently, we make a lifting of the stimulation functions (volume or surface electrodes) in order to recover an homogeneous electrostatic balance equation. The resulting model, called *current lifted monodomain model*, is a monodomain equation with a special, non local, excitation term due to the lifting. This excitation term accounts for any intra- or extra-cellular source of current and explains the apparition of the VEP phenomena in this monodomain model. The additional computational cost, with respect to the monodomain model, can be neglected since it occurs only during stimulation.

The derivation of the model is detailed in section 2 and some numerical illustrations are shown in section 3

2. Derivation of the lifted model

2.1. The original bidomain model

The bidomain model with applied currents (both in the volume and on the surface) consists in finding three functions $(u, \mathbf{v}, u_e)$ such that

$$\chi\left(C_m\partial_t u + I_{ion}(u,\mathbf{v})\right) = \nabla\cdot\left(\boldsymbol{\sigma}^{(i)}\nabla u_i\right) + I_i, \quad (1)$$

$$\chi\left(C_m\partial_t u + I_{ion}(u,\mathbf{v})\right) = -\nabla\cdot\left(\boldsymbol{\sigma}^{(e)}\nabla u_e\right) - I_e, \quad (2)$$

$$\partial_t \mathbf{v} = g(u,\mathbf{v}) \quad (3)$$

in a domain Ω_H representing the heart's volume, together with the boundary conditions

$$\mathbf{n}_H\cdot\boldsymbol{\sigma}^{(i)}\nabla u_i = \mathbf{n}_H\cdot\mathbf{j}_i, \quad \mathbf{n}_H\cdot\boldsymbol{\sigma}^{(e)}\nabla u_e = \mathbf{n}_H\cdot\mathbf{j}_e \quad (4)$$

on $\partial\Omega_H$. The unknown function $\mathbf{v}$ is the vector of variables for the ionic model; the functions u_i, u_e and $u = u_i - u_e$ are, respectively, the intracellular, extracellular and transmembrane potentials. The parameters of the equations are: the cell membrane surface-to-volume ratio χ; the capacitance per unit area of the cell membrane C_m; the intracellular and extracellular conductivity tensors $\boldsymbol{\sigma}^{(i)}$ and $\boldsymbol{\sigma}^{(e)}$. As usual they read

$$\boldsymbol{\sigma}^{(i,e)}(x) = \sum_{j=1}^{3}\boldsymbol{\sigma}_j^{(i,e)}\mathbf{a}_j(x)\mathbf{a}_j(x)^T$$

where $(\mathbf{a}_1, \mathbf{a}_2, \mathbf{a}_3)$ are three unit vectors arranged along the fiber's direction $(\mathbf{a}_1)$, laminae $(\mathbf{a}_1,\ \mathbf{a}_2)$ and perpendicular

to the laminae ($\mathbf{a}_3$). The actual conductivity coefficients are the coefficients $\boldsymbol{\sigma}_j^{(i)}$ and $\boldsymbol{\sigma}_j^{(e)}$ ($j = 1, 2, 3$).

Equation (3) is a system of ode's (function g) describing the ionic activity at the cell membrane (e.g. the Mitchell-Schaeffer or the Beeler-Reuter model).

The currents applied in the intracellular and extracellular spaces are the functions I_i and I_e and the currents applied on the surface of the heart are the functions $\mathbf{j}_i$ and $\mathbf{j}_e$.

We consider two different procedures to initiate the propagation of an action potential: applying either volume or surface currents through electrodes. It involves a compatibility condition for the problem to be well-posed, specifically:

$$\int_{\partial\Omega_H} n_H \cdot (\mathbf{j}_i + \mathbf{j}_e) + \int_{\Omega_H} (I_i + I_e) = 0. \qquad (5)$$

It is the principle of conservation of electric charge.

In this paper, we consider activation with surface current only ($I_i = I_e = 0$) for simplicity. Though the treatment of volume currents I_i and I_e is straightforward.

2.2. The weak formulation of the bidomain model

The variational formulation of equations (1) to (3) using the boundary conditions (4) reads as the evolution equations for the transmembrane potential u:

$$\chi\left(C_m \frac{d}{dt}(u, \phi_u) + (I_{ion}(u, \mathbf{v}), \phi_u)\right) + a_i(u + u_e, \phi_u) = \int_{\partial\Omega_H} \mathbf{n}_H \cdot \mathbf{j}_i \phi_u; \quad (6)$$

together with the evolution equation of the ionic variables v:

$$\frac{d}{dt}(\mathbf{v}, \phi_v) + (g(u, \mathbf{v}), \phi_v) = 0; \qquad (7)$$

and the balance equation for the intra- and extra-cellular potentials:

$$a_i(u, \phi_e) + (a_i + a_e)(u_e, \phi_e) = \int_{\partial\Omega_H} \mathbf{n}_H \cdot (\mathbf{j}_i + \mathbf{j}_e)\phi_e, \quad (8)$$

for all test functions $\phi_u \in H^1(\Omega_H)$, $\phi_v \in L^2(\Omega_H)$ and $\phi_e \in H^1(\Omega_H)$. In these equations, u_i was replaced by $u + u_e$, the notation $(\cdot, \cdot)$ stands for the L^2 scalar product, $a_i(u, v) = \int_{\Omega_H} \boldsymbol{\sigma}^{(i)} \nabla u \cdot \nabla v$ denotes the usual bilinear form on $H^1(\Omega_H)$ associated to the diffusion operator $-\nabla \cdot \boldsymbol{\sigma}^{(i)} \nabla \cdot$ and a_e is associated similarly to $-\nabla \cdot \boldsymbol{\sigma}^{(e)} \nabla \cdot$. The functional spaces are chosen according to [6].

2.3. The lifted monodomain equations

For homogeneous boundary conditions ($\mathbf{j}_i = \mathbf{j}_e = 0$), it was proved in [6] that equation (8) can be solved formally, in order to express u_e as a function of u. Hence it is possible to replace u_e by it expression in equation (6), resulting in a formulation of the bidomain model with a single equation but a more complex conductivity operator. In the equal anisotropy case, the the usual monodomain equation is recovered, which proves that the homogeneous part of the bidomain operator can be approximated by the monodomain operator (see also [7]).

In the inhomogeneous case studied here, we propose to solve for u_e in equation (8) by using a lifting technique to account for the boundary conditions: Considering that equation (8) is linear, we simply split its solution u_e into the solution u_e^1 of the homogeneous problem, that solves

$$(a_i + a_e)(u_e^1, \phi_e) = -a_i(u, \phi_e) \qquad (9)$$

and a lifting function u_e^2 that solves

$$(a_i + a_e)(u_e^2, \phi_e) = \int_{\partial\Omega_H} \mathbf{n}_H \cdot (\mathbf{j}_i + \mathbf{j}_e)\phi_e. \qquad (10)$$

Of course the solution to eq. (8) is $u_e = u_e^1 + u_e^2$.

Remark that the solution u_e^1 depends only on the transmembrane potential u while the lifting u_e^2 depends only on the total externally applied current $\mathbf{j}_i + \mathbf{j}_e$. Consequently, *the lifting u_e^2 vanishes whenever no stimulation current is applied and can be pre-computed.* The resulting equation for the evolution of u is obtained by replacing u_e by $u_e^1 + u_e^2$ in equation (6):

$$\chi\left(C_m \frac{d}{dt}(u, \phi_u) + (I_{ion}(u, \mathbf{v}), \phi_u)\right) + \underbrace{a_i(u + u_e^1(u), \phi_u)}_{\text{propagation}} = \int_{\partial\Omega_H} \mathbf{n}_H \cdot (\mathbf{j}_i + \mathbf{j}_e)\phi_u - \underbrace{a_i(u_e^2(\mathbf{j}_i + \mathbf{j}_e), \phi_u)}_{\text{applied current}}. \quad (11)$$

Equations (11) and (7), assuming that u_e^1 and u_e^2 solve equations (9) and (10), are a new statement of the complete bidomain model with externally applied currents $\mathbf{j}_i$ and $\mathbf{j}_e$.

The term $a_i(u + u_e^1(u), \phi_u)$, responsible for the propagation of the AP, is approximated by the harmonic monodomain term:

$$a_i(u + u_e^1(u), \phi_u) \simeq a_m(u, \phi_u) := \int_{\Omega_H} \boldsymbol{\sigma}^{(m)} \nabla u \cdot \nabla \phi_u$$

where $\boldsymbol{\sigma}^{(m)} = ({\boldsymbol{\sigma}^{(i)}}^{-1} + {\boldsymbol{\sigma}^{(e)}}^{-1})^{-1}$ is the usual harmonic average of the intra- and extracellular conductivities (this

approximation is justified in [7]). But the term $a_i(u_e^2(\mathbf{j}_i + \mathbf{j}_e), \phi_u)$, responsible for the non-local part of the excitation – the so-called virtual electrode polarization –, remains in the formulation.

The resulting model, called *current lifted monodomain model*, has the following weak formulation:

$$\chi\left(C_m\frac{d}{dt}(u,\phi_u)+(I_{ion}(u,\mathbf{v}),\phi_u)\right)+a_m(u,\phi_u)$$
$$=\int_{\Omega_H}\mathbf{n}_H\cdot(\mathbf{j}_i+\mathbf{j}_e)\phi_u-\int_{\Omega_H}\boldsymbol{\sigma}^{(i)}\nabla u_e^2\cdot\nabla\phi_u, \quad (12)$$

$$\frac{d}{dt}(\mathbf{v},\phi_v)+(g(u,\mathbf{v}),\phi_v)=0 \quad (13)$$

where u_e^2 solve equation (10) (recall that this equation depends only on $\mathbf{j}_i + \mathbf{j}_e$).

A strong formulation of this model would read

$$\chi\left(C_m\partial_t u+I_{ion}(u,\mathbf{v})\right)=\nabla\cdot\boldsymbol{\sigma}^{(m)}\nabla u+\mathcal{L}(\mathbf{j}_i+\mathbf{j}_e),$$
$$\partial_t\mathbf{v}+g(u,\mathbf{v})=0$$

where $\mathcal{L}(\mathbf{j}_i+\mathbf{j}_e)\in(H^1(\Omega_H))'$ is a suitable lifting of the boundary condition $\mathbf{j}_i+\mathbf{j}_e$. It is defined by duality, following the equality:

$$\langle\mathcal{L}(\mathbf{j}),\phi_u\rangle=\int_{\Omega_H}\mathbf{n}_H\cdot\mathbf{j}\phi_u-\int_{\Omega_H}\boldsymbol{\sigma}^{(i)}\nabla u_e^2\cdot\nabla\phi_u$$

with u_e^2 solution to $(a_i+a_e)(u_e^2,\phi_e)=\int_{\partial\Omega_H}\mathbf{n}_H\cdot\mathbf{j}\phi_e$, or equivalently to the elliptic equation $-\nabla\cdot(\boldsymbol{\sigma}^{(i)}+\boldsymbol{\sigma}^{(e)})\nabla u=0$ in Ω_H with the boundary condition $\mathbf{n}_H\cdot(\boldsymbol{\sigma}^{(i)}+\boldsymbol{\sigma}^{(e)})\nabla u=\mathbf{j}_i+\mathbf{j}_e$ on $\partial\Omega_H$. Describing this lifting in more details is beyond the scope of this short paper.

An important remark concerns the computation of u_e^2: we assume that the total current is modulated in time in a uniform manner with respect to space, specifically, it reads

$$\mathbf{j}(x,t):=\mathbf{j}_i(x,t)+\mathbf{j}_e(x,t)=\zeta(t)\mathbf{j}^\star(x)$$

(here $\mathbf{j}^\star$ is the space repartition of the current while ζ is the time modulation). Hence, by linearity, we have

$$u_e^2(x,t)=\zeta(t)u_e^{2,\star}(x)$$

where $u_e^{2,\star}$ solves $(a_i+a_e)(u_e^{2,\star},\phi_e)=\int_{\partial\Omega_H}\mathbf{n}_H\cdot\mathbf{j}\phi_e$: there is only one elliptic equation to be solved[1].

3. Numerical illustrations

3.1. Method

We consider a 3D domain of dimensions $1\times1\times0.3$ cm^3 for representing a slab of the heart ventricular walls. There is one small electrode (0.05×0.05 cm^2) at the center of the endocardial interface and one electrode at the epicardial surface (settings from [2]). The stimulation pulses are delivered by applying extracellular surface currents $\mathbf{j}_e$ through these two electrodes. The compatibility condition (5) is ensured and no intracellular current is applied.

We use the Mitchell-Schaeffer (MS) model that can easily match the main action potential features (conduction speed, time scales, restitution) [8], although it may not be suitable for replicating realistic responses to defibrillation shocks [1]. The parameters of the MS model are computed as in [8]. Afterward, the diffusion constant $\boldsymbol{\sigma}/(C_m\chi)$ determines the wave velocity (here we take $C_m = 1.10^{-2}$ F/m^2, $\chi = 2.10^5$ m$^-1$ and the electrical conductivities from [2]).

Both models are discretized with linear Lagrange finite elements in space and a Gear time-stepping scheme, solved with Newton's method. The finite element software MEF++[9] is used therefore.

For make stimulations, the tissue is initially at rest ($u(x,t=0)=0, \mathbf{v}(x,t=0)=0.99$). A super-threshold current is turned on at $t=0$ for a duration of 10 ms. An excitation wavefront starts propagating during the excitation and the propagation continues at the turnoff of the electrode. For break stimulations, the tissue is initially refractory ($u(x,t=0)=0, \mathbf{v}(x,t=0)=0.1$), and the current is turned on until a relative refractory state is established. At the turnoff of the electrode, the excited regions return to the resting state as they are refractory. The excitable surrounding tissue then depolarizes because of diffusion, and an excitation wavefront sweeps the cardiac domain.

3.2. Results

The four well known VEP phenomena, specifically anode/cathode make/break are observed when applying extracellular current with an endocardial electrode within the current lifted monodomain model.

In the cathode make (fig. 1) and anode make (fig. 2) stimulations, both the bidomain and the current lifted monodomain models shows similar excitation patterns (dog-bone shaped virtual cathode/anode) and similar propagation features. Propagation errors have the order of magnitude of the difference between the bidomain and the classical harmonic monodomain model, as expected from our modeling approximation.

For cathode break (fig. 3) and anode break (fig. 4) stimulations, again, the current lifted monodomain solution show the typical pattern of the cathode/anode break excitation. Very similar propagation patterns are also observed for both models.

[1] It is simply: $f(\mathbf{j})=f(\zeta(t)\mathbf{j}^\star)=\zeta(t)f(\mathbf{j}^\star)$.

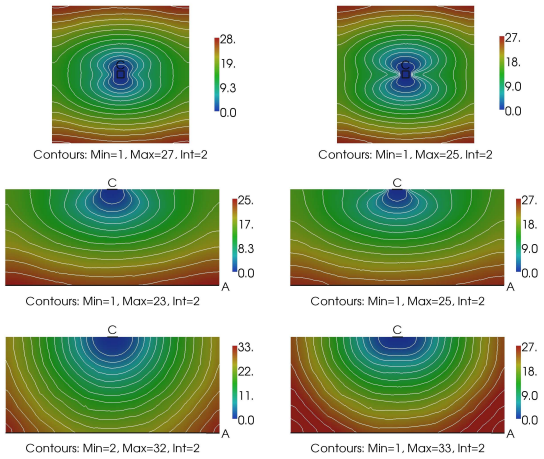

Figure 1. Cathode make, isochrons of depolarization: (left) bidomain model and (right) current lifted monodomain model.

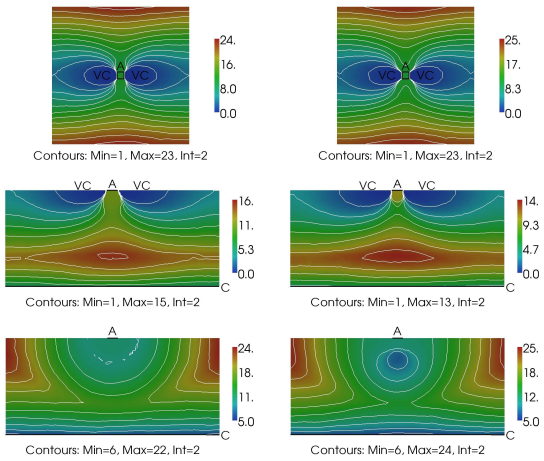

Figure 2. Anode make, isochrons of depolarization: (left) bidomain model and (right) current lifted monodomain model.

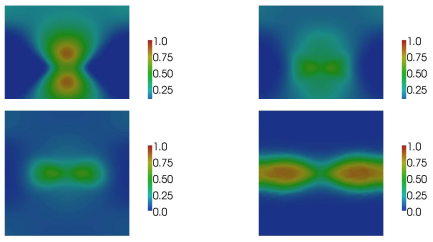

Figure 3. Cathode break: evolution of the transmembrane potential u after the turnoff of the cathode for the current lifted monodomain model (endocardial surface is shown at times 2, 6, 10, 25 ms).

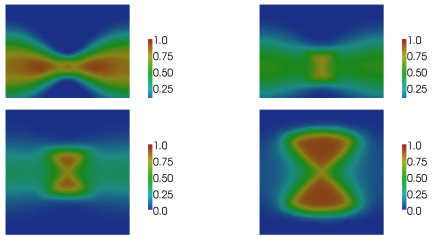

Figure 4. Anode break: evolution of the transmembrane potential u after the turnoff of the anode for the current lifted monodomain model (endocardial surface is shown at times 2, 6, 10, 25 ms.

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